EFFECT OF ORAL CYPROTERONE ACETATE ON URINARY AND SERUM FSH AND LH LEVELS IN ADULT MALES BEING TREATED FOR HYPERSEXUALITY

JANET BROTHERTON*

Schering Chemicals Ltd, Burgess Hill, Sussex, and School of Biological Sciences, University of Sussex

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Summary. A group of eighteen male hypersexual patients received 50 mg cyproterone acetate orally twice a day. Radioimmunoassays of LH and FSH were carried out at intervals on serum and 24-hr urine specimens. All the six 'pretreatment' and twenty-eight 'during-treatment' levels of urinary FSH fell within the normal range of 2 to 17 i.u. 2nd IRP-HMG/24 hr. One of the six 'pretreatment' and three of the twenty-eight 'during-treatment' levels of urinary LH were higher than the normal range of 4 to 50 i.u. 2nd IRP-HMG/24 hr. Treated as a whole, the LH levels could be regarded as showing no difference due to treatment with cyproterone acetate but if the patient with the high pretreatment level, who was also suffering from schizophrenia, was removed from the group then the LH levels during treatment showed a significant rise. The mean serum LH was 6.3 mU MRC 69/104 standard/ml with an upper limit of 14.4 mU and the mean serum FSH was 13.3 mi.u. 2nd IRP-HMG/ml with a range of 6 to 33 mi.u. All these results were within the quoted normal ranges. The mechanism of action of cyproterone acetate is discussed, taking into consideration the normal LH and FSH levels, low testosterone levels and inhibition of spermatogenesis and is compared with the actions of oestrogens, androgens, 'pure' progestagens and 'pure' anti-androgens on these parameters.

INTRODUCTION

Initial studies on the treatment of male hypersexuality with anti-androgens were with cyproterone rather than its acetate. It was discovered that cyproterone was a 'pure' anti-androgen, lacking the feedback suppression of gonadotrophin levels possessed by most compounds with progestational activity. The net effect was an increase in plasma testosterone and in FSH and LH levels (Rausch-Strooman, Petry, Hocevar, Mauss & Senge, 1970; Vosbeck & Keller, 1971; Brotherton, 1972). This is believed to be due to the direct prevention of androgenic feedback to the hypothalamus, so that more gonadotrophins are produced and hence more testosterone.

* Present address: Department of Chemotherapy, Schering A.G., 1 Berlin 65, Germany.

Current investigations are being carried out exclusively with cyproterone acetate which has strong progestational and antigonadotrophic properties in addition to its anti-androgenic action. This compound has been used experimentally since 1967 for the treatment of hypersexuality in adult males (Laschet & Laschet, 1967). Its use is known to be associated with a gradual reduction in libido and potency while spermatogenesis is also inhibited. By about 6 weeks of treatment, there is absence of ejaculate though there are no pathological changes in the testes. This contrasts with the testicular changes produced by pituitary suppression with androgens or oestrogens (Laschet & Laschet, 1971; Cooper, Ismail, Phanjoo & Love, 1972). The reduction in libido and potency takes place before the failure of spermatogenesis and returns more quickly after the cessation of treatment. This may be a reflection of the long delay of about 64 days for the complete cycle of spermatogenesis in man. Hormone assays have consistently shown that plasma testosterone levels are significantly reduced (Schoonees, Schalch & Murphy, 1971; Sorcini, Sciarra, di Silverio & Fraioli, 1971). The reduction in plasma testosterone may be as much as 50% in the first 5 days of therapy. A simultaneous rise in plasma androstenedione has been detected by Sorcini *et al.* (1971) which may be a manifestation of the local anti-androgenic action of cyproterone acetate. The effects of cyproterone acetate on gonadotrophins is less clear and the present study was specifically designed to measure the effects on LH and FSH levels.

METHODS

A group of eighteen male hypersexual patients from three clinical centres received 50 mg cyproterone acetate orally twice a day. All the patients had normal sexual characteristics and were adults aged 22 to 54 years, except for patients B.6 and B.10 who were 14 years old and suffering from Down's syndrome. Patients A.1, A.2 and A.3 were classed as manic-depressive, patients C.1, C.2 and C.3 showed a variety of aggressive sexual deviations and patient A.4 was suffering from schizophrenia. All the remaining patients were mentally subnormal. All the patients had either drawn the attention of the police to their abnormal hypersexual behaviour or were causing a sexual nuisance in a residential home for the mentally retarded.

At the start of this study, the precise nature of the episodic and diurnal fluctuations in plasma LH and FSH were not known and it was decided to estimate these gonadotrophins in 24-hr urine specimens after storage at -20°C until a batch had been accumulated. Radioimmunoassays of FSH and LH were carried out on extracts prepared by the method of Butt & Lynch (1971). Some published normal values with ranges for these assays are shown in Table 1: the results obtained by the present methods are believed to fall within these ranges.

Later, serum gonadotrophin levels were estimated. Human pituitary FSH (preparation CPDS/3) containing approximately 5000 i.u./mg by bioassay (W. R. Butt, personal communication) and human pituitary LH were iodinated by the method of Butt (1972). The antisera were prepared in rabbits and the free and bound fractions were separated by the double antibody method. The

standard for the urinary assays was the 2nd IRP-HMG: the same standard and MRC 69/104 were used for assays on blood. The MRC 69/104 standard was assumed to have a potency of 10 i.u. FSH and 25 i.u. LH/ampoule, each ampoule being equivalent to the immunoreactive FSH and LH in 0.5 mg of the NIH standard LER-907 from which it is derived (Bangham & Borth, 1972). At first, the inhibition curves for preparation MRC 69/104 were not strictly parallel to those of serum samples in the FSH immunoassay and results are therefore quoted in terms of mi.u. 2nd IRP-HMG. Latterly, the slopes approached parallelism and each mU MRC 69/104 was found to be equivalent

Table 1. Normal male urinary gonadotrophin levels by radioimmunoassay

	<i>n</i>	<i>Mean</i>	<i>Standard deviation</i>	<i>Range</i>	<i>Reference</i>
FSH	19	8.5	3.6	3 to 17	Raiti <i>et al.</i> (1969)
LH	10	31.3	10.3	17 to 50	Baghdassarian <i>et al.</i> (1970)
	220	23.9	15.5	4 to 45	Wikramanayake <i>et al.</i> (1972)
After hypophysectomy					
FSH (<i>n</i> = 7)				1.0 to 2.2	Mancini <i>et al.</i> (1971)
LH (<i>n</i> = 7)				1.4 to 2.8	

Urinary gonadotrophin levels expressed in terms of i.u. 2nd IRP-HMG/24 hr.

Table 2. Normal serum FSH and LH levels in males by radioimmunoassay

	<i>Units</i>	<i>n</i>	<i>Mean ± S.D.</i>	<i>Range</i>	<i>Reference</i>
FSH	mi.u. 2nd IRP-HMG/ml	27	17	4 to 42	Saxena <i>et al.</i> (1969)
		230	11.00 ± 0.34		Lee <i>et al.</i> (1970)
		19	7.4 ± 1.9	2 to 13	Baghdassarian <i>et al.</i> (1970)
LH	mi.u. 2nd IRP-HMG/ml	234	11.11 ± 0.25		Lee <i>et al.</i> (1970)
		27		2 to 32	Saxena <i>et al.</i> (1969)
		10	10.9 ± 4.0	6 to 23	Baghdassarian <i>et al.</i> (1970)
	mi.u. LER 907/ml	40	12.0 ± 4.0	4 to 20	Kolodny <i>et al.</i> (1972)
	μg LER 907/100 ml	48	4.3 ± 0.4	1 to 13	Rosen & Weintraub (1971)
		8	4.5 ± 3.0	3 to 7	Faiman & Winter (1971)

to 5 mi.u. 2nd IRP-HMG. In the LH assay, 1 mU MRC 69/104 standard was equivalent to about 4 mi.u. 2nd IRP-HMG. Cross-reaction by FSH in the LH radioimmunoassay was insignificant and cross-reaction by LH in the FSH estimation was not more than 5%. Normal quoted values, with ranges, for these assays are shown in Table 2. Normal results for the present methods are 8.1 ± 3.4 mi.u. 2nd IRP-HMG/ml (mean ± S.D.) with a range of 4 to 15 for FSH (sixteen samples) and 6.0 ± 4.7 mU MRC 69/104 standard/ml with a range of 2.5 to 19.0 for LH (twenty-six samples).

RESULTS

Urinary levels

Tables 3 and 4 show the LH and FSH levels respectively in 24-hr urine

specimens. Some pretreatment values were not available as the clinical trial had already started before hormone assays were arranged. The normal range of urinary FSH may be taken as 2 to 17 i.u. 2nd IRP-HMG/24 hr (Table 1). All the 'pretreatment' and all but two of the 'during-treatment' values fell within this range. Two of the 'during-treatment' values were slightly above the

Table 3. Urinary LH levels in hypersexual males

Case no.	Before treatment	Weeks (w) or months (m) of treatment								
		1 w	2 w	1 m	2 m	3 m	< 6 m	6 m	9 m	12 m
A.1	5.7			12.0 8.8			8.0 5.5	6.8		4.8
A.2			11.3					52.6		71.5
A.3								33.9		9.9
A.4*	104.0	33.6 46.8						54.6	60.2	23.4
B.1					11.4 7.0					
B.2			4.3							
B.3	22.0					7.8				
B.4										
C.1	4.7			13.1		5.5		99.8	15.9	8.9
C.2	16.5	10.6		11.0						
C.3	6.1	16.5								

Urinary LH levels expressed in terms of i.u. 2nd IRP-HMG/24 hr.

Mean, before treatment 26.5 ± 35.2 (S.D.); mean, during treatment 23.4 ± 24.1 (S.D.).

* Schizophrenic.

Table 4. Urinary FSH levels in hypersexual males

Case no.	Before treatment	Weeks (w) or months (m) of treatment								
		1 w	2 w	1 m	2 m	3 m	< 6 m	6 m	9 m	12 m
A.1	10.2			11.9 10.4			5.6 7.2	6.1		7.8
A.2			9.3					12.4		19.5
A.3								9.4		5.6
A.4*	17.2	8.5 23.5						11.6	14.3	10.3
B.1					5.8 5.2					
B.2			< 3.1							
B.3	5.8					7.1				
B.4										
C.1	2.6			9.6		4.6		8.1	4.5	9.5
C.2	5.5	10.9		4.7						
C.3	2.6	10.0								

Urinary FSH levels expressed in terms of i.u. 2nd IRP-HMG/24 hr.

Mean, before treatment 7.32 ± 5.10 (S.D.); mean, during treatment 9.16 ± 4.40 (S.D.).

* Schizophrenic.

normal range but this was not considered significant. The normal range for urinary LH is probably 4 to 50 i.u. 2nd IRP-HMG/24 hr (Table 1). One 'pretreatment' value, that of patient A.4, was significantly greater than this range at 104 i.u. but there was an isolated value of 99.8 i.u. in patient C.1 whose other values were all normal. There was a very wide spread of results

Table 5. Serum LH levels in hypersexual males

Case no.	Before treatment	Months of treatment																	
		< 1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
B.1	3.5													11.2	3.5	8.9			
B.2														8.1	5.4	6.6	n.d.		
B.3													7.1	3.5	3.0	9.2			
B.4												3.2							
B.5							6.0	13.8	5.0	7.8									
B.6*			n.d.		3.0	5.2													
B.7																			
B.8																			
B.9														6.5	11.6	7.6	6.1	8.0	
B.10*				12.3	6.1										6.0	5.4	8.5		
B.11			7.6	5.1	4.0										14.4	10.9	5.8		
			7.6																

Serum LH levels expressed in terms of mU MRC 69/104 Standard/ml.

n.d., levels not detectable.

Mean, during treatment 6.26 ± 3.50 (S.D.).

* Down's Syndrome.

Table 6. Serum FSH levels in hypersexual males

Case no.	Before treatment	Months of treatment																	
		<1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
B.1	23													9	8	10			
B.2														14	6	15			
B.3													9	9	10	11	16	14	17
B.4														10		8			
B.5																			
B.6*																			
B.7																			
B.8																			
B.9																			
B.10*																			
B.11																			

Serum FSH levels expressed in terms of m.i.u. 2nd IRP-HMG/ml.
Mean, during treatment = 13.3 ± 6.3 (S.D.).

* Down's Syndrome.

for both FSH and LH values and there was no evidence for a trend towards lower or higher values as treatment progressed. No single value was as low as the levels achieved after hypophysectomy (Mancini, Vilar, Donini & Lloret, 1971).

Treated as independent groups, the six 'pretreatment' and twenty-eight 'during-treatment' values showed no statistically significant difference (Croxtton, Cowden & Klein, 1968; Brotherton & Marcus, 1973). The mean FSH level was 7.32 ± 5.10 i.u. ($\pm$ S.D.) pretreatment, compared with 9.16 ± 4.40 i.u. ($\pm$ S.D.) during treatment and 8.5 ± 3.6 i.u. ($\pm$ S.D.) quoted by Raiti, Light & Blizzard (1969). The mean LH was 26.5 ± 35.2 i.u. ($\pm$ S.D.), compared with 23.4 ± 24.1 i.u. ($\pm$ S.D.) during treatment and 23.9 ± 15.5 i.u. ($\pm$ S.D.) quoted by Wikramanayake and his co-authors (1972).

It is possible that patient A.4 should be removed from the series of urinary results. Some patients suffering from schizophrenia have been shown to exhibit a degree of testicular damage (Hemphill, Reiss & Taylor, 1944). Primary testicular failure is usually associated with raised gonadotrophin levels and the initial LH for patient A.4 was very high. If all the results for this patient are removed from the series, the mean 'pretreatment' LH level becomes 11.04 ± 7.04 i.u. ($\pm$ S.D.) and the mean 'during-treatment' value 19.00 ± 23.40 i.u. ($\pm$ S.D.). This difference is highly significant at the 0.001 level. Similarly, the mean 'pretreatment' FSH level becomes 5.34 ± 2.79 i.u. ($\pm$ S.D.) and the mean 'during-treatment' value 8.19 ± 3.49 i.u. ($\pm$ S.D.) which is significantly different at the 0.05 level. It seems that, by the removal of the one possibly aberrant result, there is a significant rise in urinary LH and FSH levels during treatment with cyproterone acetate.

Serum levels

Tables 5 and 6 show the LH and FSH levels, respectively, in serum obtained mostly after a long period of treatment. The mean serum LH was 6.3 ± 3.5 mU MRC 69/104 standard/ml ($\pm$ S.D.) with a range of 0 to 14.4 mU/ml. The mean serum FSH was 13.3 ± 6.3 mi.u./ml ($\pm$ S.D.), with a range of 6 to 33 mi.u./ml. It is possible that patients B.6 and B.10 should be removed from the series as reduced semen counts have been reported in adults suffering from Down's syndrome (Anon., 1972). When this was done, there was no significant effect on the mean serum LH and FSH levels in this group of patients. All the serum FSH levels are within the quoted normal range (Table 2). The serum LH levels also appear to be in the normal range, taking into account the variety of standards in common use and that factors from bioassays are required to convert to the equivalent values in terms of the 2nd IRP-HMG.

DISCUSSION

This is the largest and most abundant series of LH and FSH assay results for males being treated with oral cyproterone acetate and it is difficult to compare them with other reports. Sorcini *et al.* (1971) found no change in plasma LH or FSH by radioimmunoassay, but this was after only 3 days' treatment of two patients with 300 mg/day in three doses. After 20 days' treatment of six patients with 200 mg daily, Vosbeck & Keller (1971) found only a slight

lowering of the level in the urine of LH estimated by the OAAD bioassay method after the acetone-ethanol-ammonium acetate extraction procedure, but a much more significant lowering of FSH as estimated by the ovarian augmentation bioassay method. In a trial over 16 weeks in eight men in the age range 46 to 70 (mean, 64) years, given 100 mg twice daily, Schoonees *et al.* (1971) found the maximum decrease in plasma testosterone occurred after 2 weeks of therapy, being about a tenth of the control level. There was then a rebound to a constant level of about 100 ng/100 ml compared with the normal and control means of about 400 ng/100 ml. Plasma LH did not change significantly throughout the study but plasma FSH showed a decrease which was statistically significant in the 2nd and 4th weeks, but not in the 1st and 16th weeks. These three studies are consistent with the view that cyproterone acetate has no effect on LH levels and may produce a slight decrease in FSH levels. The studies reported here show no effect on either parameter but the dosage used was the smallest so far reported. It seems likely that the antigonadotrophic activity of cyproterone acetate is very weak and only exhibited at doses of 200 to 300 mg daily.

By contrast, the antigonadotrophic activities of simple androgens and oestrogens are exhibited at much smaller doses, in that they exert a negative feedback action on the hypothalamo-pituitary axis so that gonadotrophin secretion is suppressed and hence testicular testosterone secretion is also suppressed. In very small doses, e.g. 30 to 50 μ g ethinylestradiol/day, oestrogens appear to inhibit FSH secretion more than LH secretion in women (Yen & Tsai, 1971) and men (Reiter & Kulin, 1972). During this treatment, FSH levels may decrease significantly but LH levels remain the same. In larger doses, oestrogens inhibit both LH and FSH secretion, both of which fall to basal levels. In addition to the failure of spermatogenesis, the testes show severe hyalinization.

In very small doses, androgens appear to inhibit LH secretion rather more than FSH secretion in men (Peterson, Midgley & Jaffe, 1968; Lee, Jaffe, Midgley, Kohen & Niswender, 1972). It is believed that androgens are the specific agent for the negative feedback on LH in men and there is a direct relationship between plasma testosterone and LH levels. In larger doses, both LH and FSH secretion are inhibited and the testes show hyalinization.

When progestagens are given to males and females, the dose required to cause an antigonadotrophic effect is much larger than for oestrogens and androgens. Some powerful progestagens, e.g. 17 α -hydroxyprogesterone caproate, appear to have no antigonadotrophic action in intramuscular doses of 250 mg every 3 days, and this type of weak feedback action seems to apply to all the progestagens that are structurally related to progesterone, rather than derivatives of androstane and oestrane. Progesterone itself, as a 100-mg suppository five times daily for 9 days, was required to suppress plasma LH and testosterone levels to about half the control levels in four normal males (Sundsfjord, Aakvaag & Norman, 1971). The general effect of the pregnane-type progestagens appears to be to suppress LH rather than FSH. This has been shown for medroxyprogesterone acetate in both males (Gordon and his co-authors, 1970) and in females receiving 150 mg intramuscularly every 3 months (Goldzieher,

Kleber, Moses & Rathmacher, 1970). When large doses of medroxyprogesterone acetate, i.e. 50 mg orally twice daily, were given to normal males, plasma testosterone levels only decreased to about half the control values while the simultaneous administration of the androgen, fluoxymesterone, in doses of 40 mg daily, produced a further and greater decline in plasma testosterone levels (Kirschner & Schneider, 1972).

It is now apparent that the effects of cyproterone acetate are different from those of a pure anti-androgen, i.e. cyproterone, and a pregnane-type progestagen without significant anti-androgenic effects, e.g. medroxyprogesterone acetate. It seems that the anti-androgenic component in cyproterone and its acetate is responsible for inhibition of the specific suppression of LH by androgen, so allowing the continued production of LH and, hence, of testosterone. The progestagenic component of cyproterone acetate appears to allow a partial suppression to normal values of the excess LH produced under anti-androgen alone, while the progestagenic potency of medroxyprogesterone acetate allows the direct suppression of LH to below normal values. It now seems that the suppressive effects of cyproterone acetate on libido and potency and on spermatogenesis can be achieved in the presence of normal LH and/or FSH levels.

The effect of cyproterone acetate on the testes, as shown by testicular biopsy, has been described by several workers (Ott, 1968; Markewitz, Veenema, Fingerhut, Nehme-Haily & Sommers, 1969; Städtler, 1972) and the effect on the spermatozoa in the ejaculate, when that still exists, has been described by Ott & Hoffet (1968). It is important to have pretreatment testicular biopsies for comparison as the proportion of males in mental hospitals who exhibit varying degrees of testicular atrophy is high (Johnson, 1968; Städtler, 1972) regardless of whether they are classified as suffering from schizophrenia or not. It is clear that, in previously normal males, the pathological changes induced in the testes are minimal. There is severe tubular atrophy with a narrowing of the germinal epithelium and loss of sperm-forming elements. Spermatogenesis is arrested at the stage of the spermatocytes and spermatids rarely form. There is atrophy of the Leydig cells which accounts for the decrease in plasma testosterone levels. These effects occur at 100 mg/day and appear to be dose-dependent. Complete recovery of spermatogenesis occurs on cessation of the drug, but recovery of the Leydig cells is much slower, which may account for some of the 'cures' claimed for this drug. Other progestagens have similar effects on spermatogenesis (Brotherton, 1972) although the testicular changes may be more severe, increasing in the order of pregnane-type progestagens, e.g. medroxyprogesterone acetate (Camacho, Williams & Montalvo, 1972), androstane- and oestrane-type progestagens, androgens and oestrogens. With the last two types of compounds, irreversible atrophy and hyalinization tend to occur.

It seems that, in the presence of normal FSH and LH levels, the mechanism of action of cyproterone acetate on the testes is direct. There is probably a direct competition with androgen-binding sites in the testes (Hansson & Tveter, 1971), which would account for the complete absence of androgenic stimulation of the target organs in the presence of residual significant plasma

testosterone levels. It is considered that there may also be a site of competitive inhibition at some stage in steroid synthesis after progesterone. Cyproterone acetate is structurally related to progesterone rather than testosterone. Alterations in steroid production by the testes have been shown in a significant decrease in oestradiol production (Fishman & Geller, 1970) and a large increase in androstenedione levels (Sorcini *et al.*, 1971), indicating interference with biosynthetic pathways.

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